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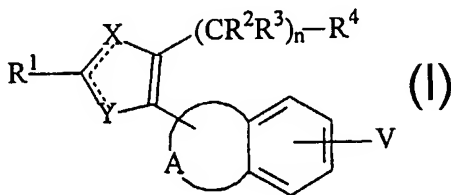
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- (71) Applicant (for all designated States except US): **JAMES BLACK FOUNDATION LIMITED** [GB/GB]; 68 Half Moon Lane, Dulwich, London SE24 9JE (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **KALINDJIAN, Sarkis, Barret** [GB/GB]; 68 Half Moon Lane, Dulwich, London SE24 9JE (GB). **BUCK, Ildiko, Maria** [GB/GB]; 68 Half Moon Lane, Dulwich, London SE24 9JE (GB). **LOW, Caroline, Minli, Rachel** [GB/GB]; 68 Half Moon Lane, Dulwich, London SE24 9JE (GB). **TOZER, Matthew, John** [GB/GB]; 68 Half Moon Lane, Dulwich, London SE24 9JE (GB).
- (74) Agents: **FISHER, Adrian, John et al.**; Carpmals & Ransford, 43 Bloomsbury Square, London WC1A 2RA (GB).
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(54) Title: **GASTRIN AND CHOLECYSTOKININ RECEPTOR LIGANDS (III)**



(57) Abstract: Compounds of formula (I) and their pharmaceutically acceptable salts are ligands at gastrin and/or cholecystokinin receptors. X and Y are independently =N-, -N(R⁵)-(R⁵ being selected from H, Me, Et, Pr, Bn, OH and -CH₂COOR⁶, wherein R⁶ represents H, Me, Et, Pr or Bn), =CH-, -O- or -S-; n is from 1 to 4; A is an optionally substituted 5- or 6- membered carbocyclic ring wherein (a) 1 or 2 C atoms may optionally be replaced by N, O and/or S atoms, (b) A is fused with the aromatic group in formula (I) to form a fused bicycle, and (c) the ring containing X and Y is linked to a C atom of A; R¹ is H or C₁ to C₁₅ hydrocarbyl wherein up to three C atoms may optionally be replaced by N, O and/or S atoms and up to three H atoms may optionally be replaced by halogen atoms; R² is selected from H, Me, Et, Pr and OH, each R² being independently selected from H, Me, Et, Pr and OH when n is greater than 1; R³ (when n is 1) is selected from H, Me, Et and Pr, or (when n is greater than 1) each R³ is independently selected from H, Me, Et and Pr, or two R³ groups on neighbouring carbon atoms are linked to form a C₃ to C₆ carbocyclic ring, or two R³ groups are absent from neighbouring carbon atoms which are linked by a double bond; or R² and R³ on the same carbon atom together represent an =O group; R⁴ is C₁ to C₁₅ hydrocarbyl wherein up to two C atoms may optionally be replaced by N, O and/or S atoms and up to three H atoms may optionally be replaced by halogen atoms; V is -CO-NH-SO₂-Ph, -SO₂-NH-CO-Ph, -CH₂OH, or a group of the formula -R⁷U, (wherein U is -COOH, tetrazolyl, -CONHOH or -SO₂H; and R⁷ is a bond; C₁ to C₆ hydrocarbylene, optionally substituted by hydroxy, amino or acetamido; -O-(C₁ to C₃ alkylene)-; -SO₂NR⁸-CHR⁹-; -CO-NR⁸-CHR⁹-, R⁸ and R⁹ being independently selected from H and methyl; or -NH-(CO)-CH₂, c being 0 or 1); or a pharmaceutically acceptable salt thereof. Compositions comprising a compound a formula (I) are also described.

Gastrin and Cholecystokinin Receptor Ligands (III)

This invention relates to gastrin and cholecystokinin (CCK) receptor ligands. (The receptor
5 previously known as the CCK_B/gastrin receptor is now termed the CCK₂ receptor). The
invention also relates to methods for preparing such ligands and to compounds which are
useful intermediates in such methods. The invention further relates to pharmaceutical
compositions comprising such ligands and methods for preparing such pharmaceutical
compositions.

10

Gastrin and the cholecystokinins are structurally related neuropeptides which exist in
gastrointestinal tissue and the central nervous system (Mutt V., *Gastrointestinal Hormones*,
Glass G.B.J., ed., Raven Press, New York, p. 169; Nisson G., *ibid.*, p. 127).

15 Gastrin is one of the three primary stimulants of gastric acid secretion. Several forms of
gastrin are found including 34-, 17- and 14-amino acid species with the minimum active
fragment being the C-terminal tetrapeptide (TrpMetAspPhe-NH₂) which is reported in the
literature to have full pharmacological activity (Tracey H.J. and Gregory R.A., *Nature*
(London), 1964, 204, 935). Much effort has been devoted to the synthesis of analogues of
20 this tetrapeptide (and the N-protected derivative Boc-TrpMetAspPhe-NH₂) in an attempt to
elucidate the relationship between structure and activity.

Natural cholecystokinin is a 33 amino acid peptide (CCK-33), the C-terminal 5 amino
acids of which are identical to those of gastrin. Also found naturally is the C-terminal
25 octapeptide (CCK-8) of CCK-33.

The cholecystokinins are reported to be important in the regulation of appetite. They
stimulate intestinal mobility, gall bladder contraction, pancreatic enzyme secretion and are
known to have a trophic action on the pancreas. They also inhibit gastric emptying and
30 have various effects in the central nervous system.

Compounds which bind to cholecystokinin and/or gastrin receptors are important because of their potential pharmaceutical use as antagonists or partial agonists of the natural peptides.

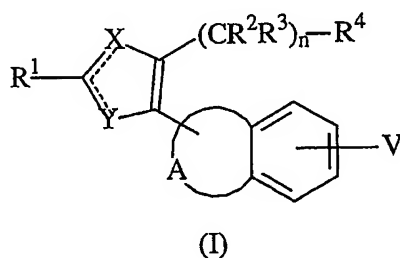
- 5 A number of gastrin antagonists have been proposed for various therapeutic applications, including the prevention of gastrin-related disorders, gastrointestinal ulcers, Zollinger-Ellison syndrome, antral G cell hyperplasia and other conditions in which lower gastrin activity or lower acid secretion is desirable. The hormone has also been shown to have a trophic action on cells and so an antagonist may be expected to be useful in the treatment
10 of cancers, particularly in the stomach and the colon.

Possible therapeutic uses for cholecystokinin antagonists include the control of appetite disorders such as anorexia nervosa and the treatment of pancreatic inflammation, biliary tract disease and various psychiatric disorders. Other possible uses are in the potentiation
15 of opiate (for example morphine) analgesia and in the treatment of cancers, especially of the pancreas. Moreover, ligands for cholecystokinin receptors in the brain (so-called CCK₂ receptors) have been claimed to possess anxiolytic activity.

PCT/GB99/03733 describes a class of compounds having gastrin antagonist activity. This
20 class of compounds is typically characterised by a 5-membered ring, preferably an imidazole or pyrrole, having two hydrocarbyl substituents and an amide or urea-type substituent.

According to the present invention, there are provided compounds of formula (I)

25



wherein X and Y are independently =N-, -N(R⁵)- (R⁵ being selected from H, Me, Et, Pr, Bn, OH and -CH₂COOR⁶, wherein R⁶ represents H, Me, Et, Pr or Bn), =CH-, -O- or -S-; n is from 1 to 4;

A is an optionally substituted 5- or 6-membered carbocyclic ring wherein

- 5 (a) 1 or 2 C atoms may optionally be replaced by N, O and/or S atoms,
(b) A is fused with the aromatic group in formula (I) to form a fused bicycle, and
(c) the ring containing X and Y is linked to a C atom of A;

R¹ is H or C₁ to C₁₅ hydrocarbyl wherein up to three C atoms may optionally be replaced by N, O and/or S atoms and up to three H atoms may optionally be replaced by halogen

10 atoms;

R² is selected from H, Me, Et, Pr and OH, each R² being independently selected from H, Me, Et, Pr and OH when n is greater than 1;

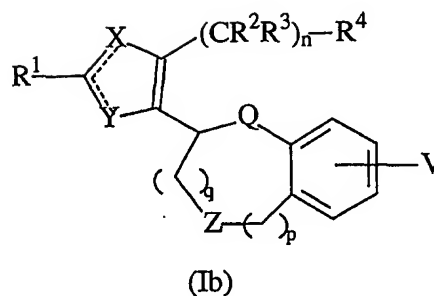
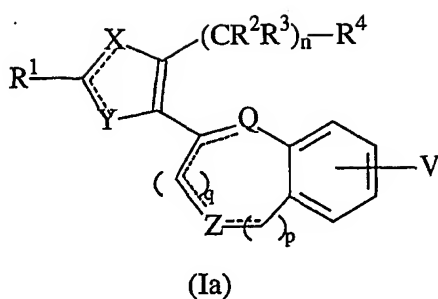
R³ (when n is 1) is selected from H, Me, Et and Pr; or (when n is greater than 1) each R³ is independently selected from H, Me, Et and Pr, or two R³ groups on neighbouring carbon
15 atoms are linked to form a C₃ to C₆ carbocyclic ring, or two R³ groups are absent from neighbouring carbon atoms which are linked by a double bond; or R² and R³ on the same carbon atom together represent an =O group;

R⁴ is C₁ to C₁₅ hydrocarbyl wherein up to two C atoms may optionally be replaced by N, O and/or S atoms and up to three H atoms may optionally be replaced by halogen atoms;

- 20 V is -CO-NH-SO₂-Ph, -SO₂-NH-CO-Ph, -CH₂OH, or a group of the formula -R⁷U, (wherein U is -COOH, tetrazolyl, -CONHOH or -SO₃H; and R⁷ is a bond; C₁ to C₆ hydrocarbylene, optionally substituted by hydroxy, amino or acetamido; -O-(C₁ to C₃ alkylene)-; -SO₂NR⁸-CHR⁹-; -CO-NR⁸-CHR⁹-, R⁸ and R⁹ being independently selected from H and methyl; or -NH-(CO)_c-CH₂-, c being 0 or 1);

- 25 or a pharmaceutically acceptable salt thereof.

Preferably, compounds of this invention are defined by formula (Ia) or (Ib).



wherein

X, Y, n, R¹, R², R³, R⁴ and V are defined as above;

5 p = 0 or 1;

q = 0 or 1;

Z and Q are independently =N-, -NH-, =CH-, -CH₂-, -S- or -O-; provided that

p + q ≠ 2; and

when p + q = 1 in formula (Ia), at least one of Z or Q is =N- or =CH-.

10

Accordingly, certain fused bicycles which are contemplated in the present invention are those derived from naphthalene, benzimidazole, benzoxazole, benzothiazole, benzothiophene, isobenzothiophene, benzofuran, isobenzofuran, indole, isoindole, chromene, isochromene, quinoline, isoquinoline, quinoxaline, quinazoline, chroman,

15 isochroman, indoline or isoindoline.

Most preferably, the fused bicycles are derived from benzimidazole or benzoxazole.

Preferably X is =N- and Y is -NH-, or *vice versa*.

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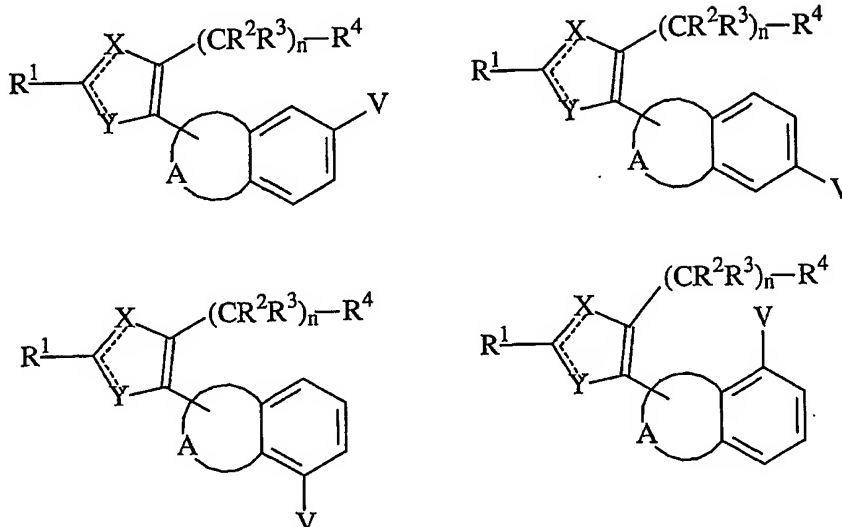
Preferably R¹ is C₁ to C₁₂ hydrocarbyl wherein one C atom may optionally be replaced by N or O and up to three H atoms may optionally be replaced by F, Cl or Br. More preferably R¹ is C₃ to C₁₂ alicyclic; phenyl, pyridyl, phenyl C₁-C₃ alkyl or pyridyl C₁-C₃ alkyl (all optionally substituted with OMe, NMe₂, CF₃, Me, F, Cl, Br or I); or C₁ to C₈ alkyl. Alicyclic groups include C₅ to C₈ cycloalkyl, C₇ to C₁₀ polycycloalkyl, C₅ to C₈ cycloalkenyl and C₇ to C₁₀ polycycloalkenyl, all optionally substituted with methyl. Phenyl C₁-C₃ alkyl includes, for example, benzyl.

25

Most preferably R¹ is cyclohexyl or bicyclooctyl.

V may be substituted at any one of the positions shown below.

5



Preferably V is $-\text{CO}-\text{NH}-\text{SO}_2-\text{Ph}$, $-\text{SO}_2-\text{NH}-\text{CO}-\text{Ph}$, $-\text{OCH}_2\text{COOH}$, tetrazolyl or $(\text{CH}_2)_s\text{COOH}$, wherein s is from 0, 1 or 2. Most preferably V is CH_2COOH , COOH or tetrazolyl.

In certain compounds according to the present invention R^2 and R^3 are H, and n is from 1 to 3.

15 In a further group of compounds according to this invention R^2 and R^3 together form an =O group and n is 1.

In certain compounds according to this invention R^4 is C_3 to C_{15} carbocyclic, optionally substituted with up to three halogen atoms. Preferably R^4 is adamantyl, cycloheptyl, 20 cyclohexyl or phenyl. Most preferably R^4 is adamantyl.

In a further group of compounds according to this invention R^4 is $-NH-R^{10}$ or $-OR^{10}$, in which R^{10} is C_3 to C_{12} carbocyclic, optionally substituted with up to three halogen atoms.

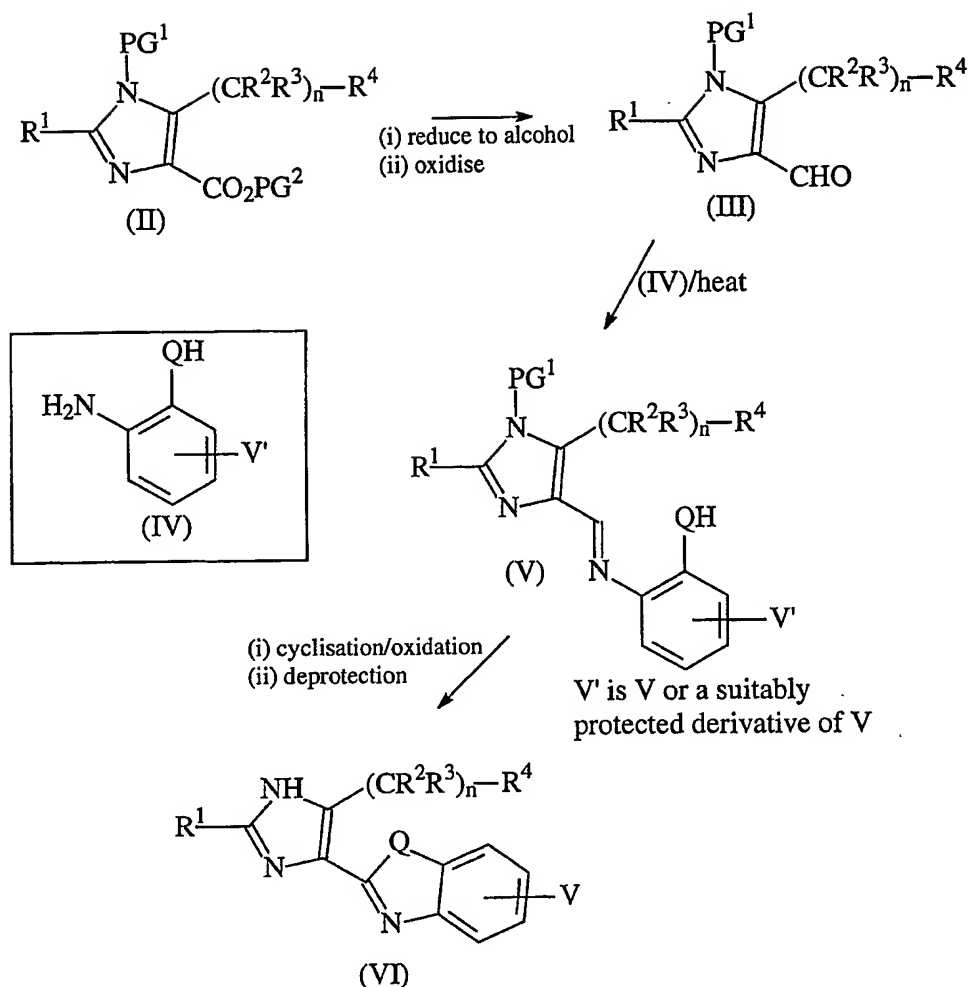
Preferably R^{10} is adamantyl, cycloheptyl, cyclohexyl or phenyl. Most preferably R^{10} is adamantyl.

Certain compounds of the present invention exist in various regioisomeric, enantiomeric,
5 tautomeric and diastereomeric forms. It will be understood that the invention comprehends
the different regioisomers, enantiomers, tautomers and diastereomers in isolation from each
other as well as mixtures.

Compounds of the present invention according to formula (Ia) wherein

- 10 (i) p is 0
- (ii) q is 0
- (iii) X is $-NH-$
- (iv) Y is $=N-$
- (v) Q is $-O-$ or $-NH-$
- 15 (vi) Z is $=N-$

may be conveniently prepared by the route exemplified in Reaction Scheme 1.



Reaction Scheme 1

Suitably protected aldehyde (III) was prepared from imidazole ester (II) using standard
 5 reduction/oxidation chemistry e.g. $LiAlH_4$ reduction of a benzyl ester followed by
 oxidation with MnO_2 . A Mannich condensation of aldehyde (III) with amine (IV) furnishes
 imine (V). Finally, heating, oxidation (with for example NiO_2) and deprotection affords the
 requisite fused bicycle (VI). It will be readily apparent to the skilled person that other
 compounds according to formula (I), (Ia) or (Ib) can be prepared by known heterocycle
 10 syntheses starting from aldehyde (III), or suitable derivatives thereof.

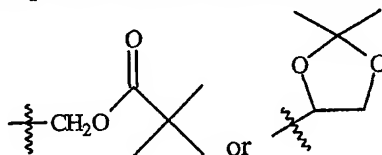
Hence, the present invention provides methods of making compounds according to formula
 (I).

The invention also comprehends derivative compounds ("pro-drugs") which are degraded *in vivo* to yield the species of formula (I). Pro-drugs are usually (but not always) of lower potency at the target receptor than the species to which they are degraded. Pro-drugs are particularly useful when the desired species has chemical or physical properties which make its administration difficult or inefficient. For example, the desired species may be only poorly soluble, it may be poorly transported across the mucosal epithelium, or it may have an undesirably short plasma half-life. Further discussion of pro-drugs may be found in Stella, V. J. *et al.*, "Prodrugs", *Drug Delivery Systems*, 1985, pp. 112-176, and *Drugs*, 1985, **29**, pp. 455-473.

10

Pro-drug forms of the pharmacologically-active compounds of the invention will generally be compounds according to formula (I) having an acid group which is esterified or amidated. Included in such esterified acid groups are groups of the form $-\text{COOR}^a$, wherein R^a is C_1 to C_5 alkyl, phenyl, substituted phenyl, benzyl, substituted benzyl, or one of the following:

15



Amidated acid groups include groups of the formula $-\text{CONR}^b\text{R}^c$, wherein R^b is H, C_1 to C_5 alkyl, phenyl, substituted phenyl, benzyl, or substituted benzyl, and R^c is $-\text{OH}$ or one of the groups just recited for R^b .

20

Compounds of formula (I) having an amino group may be derivatised with a ketone or an aldehyde such as formaldehyde to form a Mannich base. This will hydrolyse with first order kinetics in aqueous solution.

25 Another aspect of the present invention is a pharmaceutical composition comprising a compound of formula (I) substantially as described herein before with a pharmaceutically acceptable diluent or carrier.

Yet another aspect of the present invention is a method of making a pharmaceutical composition comprising a compound of formula (I) substantially as described herein

30

before, comprising mixing said compound with a pharmaceutically acceptable diluent or carrier.

Pharmaceutically acceptable salts of the acidic or basic compounds of the invention can of course be made by conventional procedures, such as by reacting the free base or acid with
5 at least a stoichiometric amount of the desired salt-forming acid or base.

Pharmaceutically acceptable salts of the acidic compounds of the invention include salts with inorganic cations such as sodium, potassium, calcium, magnesium, and zinc, and salts with
10 organic bases. Suitable organic bases include N-methyl-D-glucamine, arginine, benzathine, diolamine, olamine, procaine and tromethamine.

Pharmaceutically acceptable salts of the basic compounds of the invention include salts derived from organic or inorganic acids. Suitable anions include acetate, adipate, besylate, bromide, camsylate, chloride, citrate, edisylate, estolate, fumarate, gluceptate, gluconate,
15 glucuronate, hippurate, hyclate, hydrobromide, hydrochloride, iodide, isethionate, lactate, lactobionate, maleate, mesylate, methylbromide, methylsulfate, napsylate, nitrate, oleate, pamoate, phosphate, polygalacturonate, stearate, succinate, sulfate, sulfosalicylate, tannate, tartrate, terephthalate, tosylate and triethiodide.

20

It is anticipated that the compounds of the invention can be administered by oral or parenteral routes, including intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical administration, and inhalation.

25 For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules or as an aqueous solution or suspension.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and
30 preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate and lactose. Corn starch and alginic acid are suitable disintegrating

agents. Binding agents may include starch and gelatine. The lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

5

Capsules for oral use include hard gelatine capsules in which the active ingredient is mixed with a solid diluent and soft gelatine capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

- 10 For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-
15 pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

Effective doses of the compounds of the present invention may be ascertained by conventional methods. The specific dosage level required for any particular patient will
20 depend on a number of factors, including severity of the condition being treated, the route of administration and the weight of the patient. In general, however, it is anticipated that the daily dose (whether administered as a single dose or as divided doses) will be in the range 0.001 to 5000 mg per day, more usually from 1 to 1000 mg per day, and most usually from 10 to 200 mg per day. Expressed as dosage per unit body weight, a typical dose will be expected
25 to be between 0.01 $\mu\text{g/kg}$ and 50 mg/kg , especially between 10 $\mu\text{g/kg}$ and 10 mg/kg , eg. between 100 $\mu\text{g/kg}$ and 2 mg/kg .

- In a further aspect of the present invention there are provided pharmaceutical compositions comprising a compound according to formula (I) and a proton pump inhibitor.
30 Compositions comprising a CCK/gastrin antagonist and a proton pump inhibitor are described in International patent application WO93/12817, incorporated herein by reference.

In one aspect of the present invention the proton pump inhibitor is

omeprazole which is 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole;

5 BY308;

SK & 95601 which is 2-[[3-chloro-4-morpholino-2-pyridyl)methyl]sulfinyl]-5-methoxy-(1H)-benzimidazole;

SK & 96067 which is 3-butyryl-4-(2-methylphenylamino)-8-methoxyquinoline;

5-trifluoromethyl-2-[4-methoxy-3-methyl-2-pyridyl-methyl]-thio-[1H]-

10 benzimidazole;

or pharmaceutically acceptable salts thereof.

These proton pump inhibitors are described and claimed in US Patents 4,472,409 and 4,255,431. These patents are incorporated herein by reference.

15

In a further aspect of the present invention, the proton pump inhibitor is

lansoprazole which is 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole;

20 pantoprazole which is 5-(difluoromethoxy)-2-[[3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole;

perprazole;

rabeprazole which is 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulfinyl]-1H-benzimidazole;

[[4-(2,2,2-trifluoroethoxy)-3-methyl-2-pyridyl]-methyl]sulfenamide;

25 (Z)-5-methyl-2-[2-(1-naphthyl)ethenyl]-4-piperidinopyridine HCl;

2-(4-cyclohexyloxy-5-methylpyridin-2-yl)-3-(1-naphthyl)-1-propanol;

methyl 2-cyano-3-(ethylthio)-3-(methylthio)-2propenoate;

2-((4-methoxy-2-pyridyl)methylsulphanyl)-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole sodium;

30 2-[[[4-(2,2,3,3,4,4,4-heptafluorobutoxy)-2-pyridyl]methyl]sulfinyl]-1H-thieno [3,4-d]imidazole;

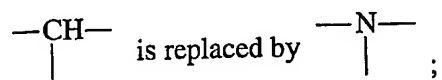
- 2-[[[4-(2,2,2-trifluoroethoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole;
- 2-[[[4-(2,2,2-trifluoroethoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole;
- 5 2-methyl-8-(phenylmethoxy)-imidazo(1,2-A)-pyridine-3-acetonitrile;
(2-((2-dimethylaminobenzyl)sulfinyl)-benzimidazole);
4-(N-allyl-N-methylamino)-1-ethyl-8-((5-fluoro-6-methoxy-2-benzimidazolyl)sulfinylmethyl)-1-ethyl 1,2,3,4-tetrahydroquinolone;
- 2-[[[4-(2-dimethylaminophenyl)methyl]sulfinyl]-4,7-dimethoxy-1H-benzimidazole;
- 10 2-[(2-(2-pyridyl)phenyl)sulfinyl]-1H-benzimidazole;
(2-[(2-amino-4-methylbenzyl)sulfinyl]-5-methoxybenzo[d]imidazole;
(4-(2-methylpyrrol-3-yl)-2-guanidisoctazole);
4-(4-(3-(imidazole)propoxy)phenyl)-2-phenylthiazole;
(E)-2-(2-(4-(3-(dipropylamino)butoxy)phenyl)-ethenyl)benzoxazole;
- 15 (E)-2-(2-(4-(3-(dipropylamino)propoxy)phenyl)ethenyl)-benzothiazole;
Benzeneamine, 2-[[[4-(5-methoxy-1H-benzimidazol-2-yl)sulfinyl]methyl]-4-methyl-; Pumulacidin A;
2,3-dihydro-2-methoxycarbonylamino-1,2-benzisothiazol-3-one;
2-(2-ethylaminophenylmethylsulfinyl)-5,6-dimethoxybenzimidazole;
- 20 2-methyl-8-(phenylmethoxy)imidazo[1,2-a]pyridine-3-acetonitrile;
3-amino-2-methyl-8-phenylmethoxyimidazo[1,2-a]pyrazine HCl;
2-[[[4-(3-chloro-4-morpholino-2-pyridyl)methyl]sulfinyl]-5-methoxy-(1H)-benzimidazole;
- [3-butyryl-4-(2-methylphenylamino)-8-methoxy-quinoline];
- 25 2-indanyl 2-(2-pyridyl)-2-thiocarbamoylacetate HCl;
2,3-dihydro-2-(2-pyridinyl)-thiazolo (3,2-a) - benzimidazole;
3-cyanomethyl-2-methyl-8-(3-methyl-2-butenyloxy)- (1,2-a)imidazopyridine;
zinc L-carnosine;
- or pharmaceutically acceptable salts thereof.

Rabeprazole is described in US patent 5,045,552. Lansoprazole is described in US patent 4,628,098. Pantoprazole is described in US patent 4,758,579. These patents are incorporated herein by reference.

- 5 Preferably, the proton pump inhibitor is selected from (RS)-rabeprazole, (RS)-omeprazole, lansoprazole, pantoprazole, (R)-omeprazole, (S)-omeprazole, perprazole, (R)-rabeprazole, (S)-rabeprazole, or the alkaline salts thereof. The alkaline salts may be, for example, the lithium, sodium, potassium, calcium or magnesium salts.
- 10 Compositions of this invention comprising a compound of formula (I) and a proton pump inhibitor may be administered as described above. Preferably the dose of each of the active ingredients in these compositions will be equal to or less than that which is approved or indicated in monotherapy with said active ingredient.
- 15 In another aspect of this invention, there is provided a kit comprising a compound of formula (I) and a proton pump inhibitor. The kit is useful as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from gastrointestinal disorders.
- 20 In yet a further aspect of the present invention there is provided a method of making a pharmaceutical composition comprising a compound of formula (I) substantially as described herein before and a proton pump inhibitor, comprising mixing said compound and said proton pump inhibitor with a pharmaceutically acceptable carrier or diluent.
- 25 The term "hydrocarbyl" is used herein to refer to monovalent groups consisting of carbon and hydrogen. Hydrocarbyl groups thus include alkyl, alkenyl and alkynyl groups (in both straight and branched chain forms), cycloalkyl (including polycycloalkyl), cycloalkenyl and aryl groups, and combinations of the foregoing, such as alkylcycloalkyl, alkylpolycycloalkyl, alkylaryl, alkenylaryl, alkynylaryl, cycloalkylaryl and cycloalkenylaryl
- 30 groups.

Where reference is made to a carbon atom of a hydrocarbyl group being replaced by a N, O

or S atom, what is intended is that



or that $\text{---CH}_2\text{---}$ is replaced by ---O--- or ---S--- .

5 A "carbocyclic" group, as the term is used herein, comprises one or more closed chains or rings, which consist entirely of carbon atoms. Carbocyclic groups thus include aryl groups (such as phenyl, naphthyl, indanyl, fluorenyl, (1,2,3,4)-tetrahydronaphthyl, indenyl and isoindenyl, and substituted derivatives thereof), and also alicyclic groups. The term "alicyclic group" refers to a carbocyclic group which does not contain an aromatic ring, and
10 thus includes groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, adamantyl, norbornyl, bicyclo[2.2.2]octyl, norbornenyl and bicyclo[2.2.2]octenyl, and also groups (such as adamantanemethyl and methylcyclohexyl) which contain both alkyl or alkenyl groups in addition to cycloalkyl or cycloalkenyl moieties.

15

The term "aryl" is used herein to refer to an aromatic group, such as phenyl or naphthyl, or a heteroaromatic group, such as pyridyl, pyrrolyl, or furanyl.

The term "alkyl" is used herein to refer to both straight and branched chain forms.

20

When reference is made herein to a substituted carbocyclic group (such as substituted phenyl) or a substituted heterocyclic group, the substituents are preferably from 1 to 3 in number and selected from C_1 to C_6 alkyl, C_1 to C_6 alkoxy, thio, C_1 to C_6 alkylthio, carboxy, carboxy(C_1 to C_6)alkyl, formyl, C_1 to C_6 alkylcarbonyl, C_1 to C_6 alkylcarbonylalkoxy, nitro,
25 trihalomethyl, hydroxy, C_1 to C_6 alkylhydroxy, hydroxy(C_1 to C_6)alkyl, amino, C_1 to C_6 alkylamino, di(C_1 to C_6 alkyl)amino, aminocarboxy, C_1 to C_6 alkylaminocarboxy, di(C_1 to C_6 alkyl)aminocarboxy, aminocarboxy(C_1 to C_6)alkyl, C_1 to C_6 alkylaminocarboxy(C_1 to C_6)alkyl, di(C_1 to C_6 alkyl)aminocarboxy(C_1 to C_6)alkyl, C_1 to C_6 alkylcarbonylamino, C_5 to C_8 cycloalkyl, C_5 to C_8 cycloalkyl(C_1 to C_6)alkyl, C_1 to C_6 alkylcarbonyl(C_1 to C_6
30 alkyl)amino, aryl, aryl(C_1 to C_6)alkyl, (C_1 to C_6 alkyl)aryl, halo, C_1 to C_6 alkylhalo, sulphamoyl, tetrazolyl and cyano.

Most usually, substituents will be selected from C₁ to C₆ alkyl, C₁ to C₆ alkoxy, thio, C₁ to C₆ alkylthio, carboxy, carboxy(C₁ to C₆)alkyl, formyl, C₁ to C₆ alkylcarbonyl, C₁ to C₆ alkylcarbonylalkoxy, nitro, trihalomethyl, hydroxy, C₁ to C₆ alkylhydroxy, hydroxy(C₁ to C₆)alkyl, amino, C₁ to C₆ alkylamino, di(C₁ to C₆ alkyl)amino, aminocarboxy, C₁ to C₆ alkylaminocarboxy, di(C₁ to C₆ alkyl)aminocarboxy, aminocarboxy(C₁ to C₆)alkyl, C₁ to C₆ alkylaminocarboxy(C₁ to C₆)alkyl, di(C₁ to C₆ alkyl)aminocarboxy(C₁ to C₆)alkyl, C₁ to C₆ alkylcarbonylamino, C₅ to C₈ cycloalkyl, C₅ to C₈ cycloalkyl(C₁ to C₆)alkyl, C₁ to C₆ alkylcarbonyl(C₁ to C₆ alkyl)amino, halo, C₁ to C₆ alkylhalo, sulphamoyl, tetrazolyl and cyano.

The term "halogen" is used herein to refer to any of fluorine, chlorine, bromine and iodine. Most usually, however, halogen substituents in the compounds of the invention are chlorine and fluorine substituents.

15

The term "suitably protected" used herein refers to the use of any suitable protecting group to protect a functional group. Such protecting groups are denoted as PG, PG¹, PG², PG³ etc. in the Reaction Scheme illustrated above. Suitable protecting groups will be readily apparent to the skilled person and may be found in, for example, Kocienski, *Protecting Groups*, Thieme, New York, 1994. For example, in the case of hydroxyl groups, suitable protecting groups may include esters, ethers (e.g. silyl ethers or alkyl ethers) or acetals. Some specific examples of typical hydroxyl protecting groups are allyl, Aloc, benzyl, BOM, t-butyl, trityl, TBS, TBDPS, TES, TMS, TIPS, PMB, MEM, MOM, MTM, and THP. In the case of nitrogen atoms, suitable protecting groups may include Boc, Aloc, Troc, benzyl, allyl, Fmoc or silyl. In the case of carboxylic acids, suitable protecting groups may include esters (e.g. benzyl, allyl, methyl or ethyl esters).

The invention is now further illustrated by means of the following Examples. All reactions were performed under an atmosphere of dry argon unless otherwise stated. Anhydrous dichloromethane (DCM) was freshly distilled from calcium hydride. Anhydrous tetrahydrofuran (THF) and N,N-dimethylformamide (DMF) were used.

Example 1

2-[5-(Adamantan-1-yloxymethyl)-2-cyclohexyl-1H-imidazole-4-yl]-benzooxazole-5-carboxylic acid

- 5 **Step a.** *(Adamantan-1-yloxy)-acetic acid.* A mixture of (adamantan-1-yloxy)-acetic acid ethyl ester (A.F. Noels et al. Tetrahedron, 1982, **38**, 2733) (7.29g, 29mmol) and potassium hydroxide (2.60g, 46mmol) in water-ethanol (1:2 mixture, 180ml) was heated at reflux for 2h. The mixture was cooled, then concentrated in vacuum and acidified with concentrated hydrochloric acid. The resultant white precipitate was dissolved in ethyl acetate (200ml).
- 10 The solution was washed with brine (2x200ml), dried (MgSO₄) and the solvent was evaporated to afford a white crystalline solid (5.85g 92%). ¹H NMR (300 MHz, CDCl₃) 4.08 (2H, s), 2.20-1.58 (15H, m).

- Step b.** *4-(Adamantan-1-yloxy)-3-oxo-2-(triphenyl-^δ-phosphanylidene)-butyric acid benzyl ester.* Oxalyl chloride (18.6ml, 0.214mol) was added to a solution of the product of step a (39.13g, 0.178mol) in DCM (800ml) containing catalytic amount of DMF at room temperature. The mixture was stirred at ambient temperature for 1h, then the solvent was evaporated. The residue was dissolved in benzene (100ml) and added dropwise to a solution of benzyl (triphenylphosphoranylidene)acetate (72.9g, 0.178mol) and N,O-
- 20 bis(trimethylsilyl)acetamide (53.2ml, 0.215mol) in benzene (300ml) at 0°C. The mixture was allowed to warm to room temperature, and stirred for 16h. The reaction mixture was diluted with ethyl acetate (500ml), washed with 5% aqueous potassium hydrogen sulfate (500ml), 10% sodium carbonate (500ml), brine (300ml), dried (MgSO₄) and the solvent was evaporated. The residue was triturated with diethyl ether to afford a white solid
- 25 (93.83g, 98%). ¹H NMR (300MHz, CDCl₃) 7.64-6.94 (20H, m), 4.74 (2H, s), 4.72 (2H, s), 2.08-1.57 (15H, m).

- Step c.** *5-(Adamantan-1-yl-oxymethyl)-2-cyclohexyl-1H-imidazole-4-carboxylic acid benzyl ester.* To a vigorously stirred solution of the product of step b (33.0g, 55.0mmol) in
- 30 DCM/water (1:1 mixture, 800ml) were added tetrabutylammonium bromide (1.77g, 5.50mmol) and potassium peroxymonosulfate (OXONE) (67.4g, 110mmol) at 0°C. The mixture was stirred at ambient temperature for 48h, the organic layer was separated,

washed with water (3x200ml), brine (200ml), dried (MgSO₄) and the solvent was evaporated in vacuum. To a slurry of the residue (1:1 mixture of 4-(adamantan-1-yloxy)-2,3-dioxo-butyric acid benzyl ester monohydrate and triphenylphosphine oxide) and ammonium acetate (42.4g, 550mmol) in acetic acid (250ml) was added
5 cyclohexanecarboxaldehyde (8.0ml, 66.0mmol). The mixture was stirred in an oil bath heated at 70°C for 2h. The solution was cooled to room temperature and the acetic acid was evaporated in vacuum. The residue was suspended in ethyl acetate (200ml) and the precipitated ammonium acetate was filtered and washed with ethyl acetate (2x50ml). The filtrate was washed with saturated sodium bicarbonate (2x200ml) and brine (200ml). The
10 organic layer was dried (MgSO₄) and the solvent was evaporated. The crude product was purified by flash column chromatography (silica, DCM/ethyl acetate 4:1) to afford a pale orange foam, which was recrystallized from hexane-ethyl acetate 1:1 to afford the product as an off-white solid (13.6g, 55%). ¹H NMR (CDCl₃) 7.40 (5H, m), 5.30 (2H, s), 4.76 (2H, br s), 2.79 (1H, m), 2.14 (3H, br s), 2.05 (2H, m), 1.85-1.26 (20H, m).

15

Step d. 5-(Adamantan-1-yloxymethyl)-1-benzyl-2-cyclohexyl -1H-imidazole-4-carboxylic acid benzyl ester. To the solution of the product of step c (2.1g, 4.69mmol) in DMF (15ml) was added sodium hydride (60% dispersion in mineral oil, 225mg, 5.62mmol). The mixture was stirred at ambient temperature for 0.5h then benzyl bromide (0.67ml, 20 5.62mmol) was added. The reaction mixture was stirred at ambient temperature for 16h, then partitioned between ethyl acetate and water. The organic layer was washed with 1M HCl, saturated sodium hydrogen carbonate, and brine, dried (MgSO₄) and evaporated. The major isomer was isolated by flash chromatography (silica, DCM/ethyl acetate 92:8) (2.15g, 85%). ¹H NMR (300 MHz, CDCl₃) 7.45 (2H, dd), 7.37-7.27 (6H, m), 6.98 (2H, m),
25 5.37 (2H, s), 5.28 (2H, s), 4.68 (2H, s), 2.52 (1H, m), 2.14 (2H, br s), 2.04 (3H, br s), 1.78-1.35 (17H, m), 1.28-1.14 (3H, m).

Step e. [5-(Adamantan-1-yloxymethyl)-1-benzyl-2-cyclohexyl-1H-imidazole-4-yl]-
30 methanol. Lithium aluminium hydride (300mg, 8.20mmol) was added in small portions to an ice cooled solution of the product of step d (2.20g, 4.10mmol) in THF (25ml). The suspension was allowed to warm to ambient temperature and stirred for 2h. The reaction

mixture was cooled with ice and sodium hydroxide solution (2N, 1.6ml) was slowly added. The reaction mixture was diluted with ethyl acetate (50ml) and filtered through a plug of Celite and MgSO₄. The filtrate was evaporated under reduced pressure and the residue was crystallised from diethyl ether to afford white crystals (1.40g, 79%). ¹H NMR (300 MHz, CDCl₃) 7.28 (3H, m), 7.00 (2H, m), 5.18 (2H, s), 4.63 (2H, d), 4.34 (2H, s), 2.64 (1H, br m), 2.50 (1H, m), 2.13 (3H, br s), 1.72-1.54 (19H, m), 1.25 (3H, m).

Step f. *5-(Adamantan-1-ylloxymethyl)-1-benzyl-2-cyclohexyl -1H-imidazole-4-carbaldehyde*. To a solution of the product of step e (1.40g, 3.22mmol) in dioxan (40ml) was added manganese(IV) oxide (1.45g, 16.7mmol) and the mixture was stirred at ambient temperature for 3h. The reaction mixture was filtered through Celite and the filtrate was evaporated to afford a colourless foam (1.38g, 99%). ¹H NMR (300 MHz, CDCl₃) 9.99 (1H, s), 7.32 (3H, m), 7.00 (2H, d), 5.31 (2H, s), 4.74 (2H, s), 2.51 (1H, m), 2.13 (3H, br s), 1.78-1.57 (19H, m), 1.22 (3H, m).

15

Step g. *3-[[5-(Adamantan-1-ylloxymethyl)-1-benzyl-2-cyclohexyl -1H-imidazole-4-ylmethylene]-amino]-4-hydroxy-benzoic acid methyl ester*. To a solution of the product of step f (432mg, 1.00mmol) in ethanol (5ml) was added 3-amino-4-hydroxy-benzoic acid methyl ester. The mixture was heated at reflux for 5min, then left to stand at ambient temperature for 16h. The crystals were filtered, washed with ethanol and dried (470mg, 81%). ¹H NMR (300 MHz, CDCl₃) 8.83 (1H, s), 7.99 (1H, s), 7.86 (1H, dd), 7.35 (3H, m), 7.02 (3H, m), 5.30 (2H, s), 4.75 (2H, s), 3.89 (3H, s), 2.55 (1H, m), 2.15 (3H, br s), 1.81-1.55 (19H, m), 1.25 (3H, m).

Step h. *2-[5-(Adamantan-1-ylloxymethyl)-1-benzyl-2-cyclohexyl -1H-imidazole-4-yl]-benzooxazole-5-carboxylic acid methyl ester*. To a solution of the product of step g (310mg, 0.53mmol) in DCM (10ml) was added nickel peroxide (500mg). The mixture was stirred at ambient temperature for 3h, filtered through Celite and the filtrate was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, DCM/ethyl acetate 95:5) to afford white solid (200mg, 65%). ¹H NMR (300 MHz, CDCl₃) 8.39 (1H, s), 8.04 (1H, dd), 7.61 (1H, d), 7.34 (3H, m), 7.05 (3H, d), 5.37 (2H, s), 5.01 (2H, s), 3.96 (3H, s), 2.59 (1H, m), 2.15 (3H, br s), 1.84-1.56 (19H, m), 1.24 (3H, m).

Step i. 2-[5-(Adamantan-1-yloxymethyl)-2-cyclohexyl-1H-imidazole-4-yl]-benzooxazole-5-carboxylic acid methyl ester. To a solution of the product of step h (197mg, 0.34mmol) in acetic acid (5ml) was added 10% palladium on charcoal (20mg). The mixture was stirred under a hydrogen atmosphere for 16h. The catalyst was filtered, the filtrate was evaporated under reduced pressure. The residual acetic acid was removed by co-evaporation with toluene and then chloroform to afford a white solid (165mg, 99%). ¹H NMR (300 MHz, CDCl₃) 9.35 (1H, br s), 8.40 (1H, s), 8.04 (1H, d), 7.59 (1H, d), 5.06 (2H, s), 3.95 (3H, s), 2.82 (1H, m), 2.22 (3H, br s), 2.11 (2H, m), 1.88 (6H, br s), 1.72-1.57 (11H, m), 1.42-1.26 (3H, m).

Step k. To a solution of the product of step i (165mg, 0.34mmol) in THF (3ml) was added lithium hydroxide monohydrate (70mg, 1.68mmol) and water (1.5ml). The mixture was stirred at ambient temperature for 16h, then heated at reflux for 3h. The THF was removed by evaporation under reduced pressure, the residue was diluted with water and acidified (1N HCl, pH=3). The precipitate was filtered, washed with water, dried to afford a beige solid (117mg, 74%). ¹H NMR (300 MHz, d₆-DMSO) 13.00 (2H, br s), 8.20 (1H, s), 7.98 (1H, d), 7.80 (1H, d), 4.87 (2H, s), 2.77 (1H, m), 2.12 (3H, br s), 1.95-1.58 (19H, m), 1.31 (3H, m). The acid was converted to the N-methyl-D-glucamine salt and lyophilised from water/dioxan. Found: C 57.84, H 7.87, N 7.69%; C₃₅H₅₀N₄O₉·2.2 H₂O requires: C 57.78, H 7.80, N 7.70%.

Example 2

2-[5-(Adamantan-1-yloxymethyl)-2-cyclohexyl-1H-imidazole-4-yl]-benzooxazole-6-carboxylic acid

The title compound was prepared according to the procedure of Example 1, with the modification that 4-amino-3-hydroxy-benzoic acid methyl ester was used in step g instead of 3-amino-4-hydroxy-benzoic acid methyl ester. ¹H NMR (300 MHz, d₆-DMSO) 13.01 (2H, br s), 12.40 (1H, br s), 8.18 (1H, s), 7.95 (1H, d), 7.75 (1H, d), 4.89 (2H, s), 2.73 (1H, m), 2.12 (3H, br s), 1.93 (2H, m), 1.80-1.54 (17H, m), 1.36-1.21 (3H, m). The acid was

converted to the N-methyl-D-glucamine salt and lyophilised from water/dioxan. Found: C 59.60, H 7.89, N 8.05%; $C_{35}H_{50}N_4O_9 \cdot 2.0 H_2O$ requires: C 59.47, H 7.70, N 7.93%.

Example 3

5 2- [5-(Adamantan-1-yloxymethyl)-2-cyclohexyl -1H-imidazole-4-yl]-1H- benzoimidazole-5-carboxylic acid

Step a. 2-[5-(Adamantan-1-yloxymethyl)-1-benzyl-2-cyclohexyl-1H-imidazole-4-yl]-1H-benzoimidazole-5-carboxylic acid methyl ester. To a solution of 5-(adamantan-1-yloxymethyl)-1-benzyl-2-cyclohexyl -1H-imidazole-4-carbaldehyde (Example 1, step f) (320mg, 0.74mmol) in ethanol (5ml) was added 3,4-diamino-benzoic acid methyl ester (123mg, 0.74mmol). The mixture was heated at reflux for 5min, then kept at ambient temperature for 16h. The solvent was evaporated; the residue was dissolved in nitrobenzene (3ml) and placed in an oil bath at 150°C for 1h. The solution was cooled to ambient temperature and purified by flash column chromatography (silica, DCM/ethyl acetate 9:1 to 8:2) to afford a colourless foam (255mg, 60%). 1H NMR (300 MHz, $CDCl_3$) 11.35 and 11.25 (1H, 2xbr s), 8.42 and 8.05 (1H, 2xs), 7.90 and 7.70 (2H, 2xm), 7.30 (4H, m), 7.06 (2H, m), 5.29 (2H, s), 5.12 and 5.09 (2H, 2xs), 3.92 (3H, s), 2.50 (1H, m), 2.13 (3H, br s), 1.81-1.55 (19H, m), 1.23 (3H, m).

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Step b. 2-[5-(Adamantan-1-yloxymethyl)-2-cyclohexyl-1H-imidazole-4-yl]-1H-benzoimidazole-5-carboxylic acid methyl ester. The product of step a (250mg, 0.43mmol) was hydrogenolysed using essentially the same procedure as in Example 1, step i to afford an off-white solid (179mg, 85%). 1H NMR (300 MHz, $CDCl_3$) 8.27 (1H, br s), 7.98 (1H, d), 7.60 (1H, br s), 4.94 (2H, s), 3.95 (3H, s), 2.74 (1H, m), 2.20 (3H, br s), 2.02-1.57 (19H, m), 1.29 (3H, m).

Step c. To a solution of the product of step b (170mg, 0.35mmol) in ethanol (3ml) was added a solution of potassium hydroxide (80mg, 1.40mmol) in water. The mixture was heated at reflux for 4h, cooled and the ethanol was evaporated. The residue was diluted with water (5ml) and acidified (1N HCl, pH=3). The precipitate was filtered, washed with water and dried to afford an off-white solid (130mg, 74%). 1H NMR (300 MHz, d_6 -

DMSO) 8.19 (1H, s), 7.87 (1H, d), 7.68 (1H, d), 5.00 (2H, s), 2.94 (1H, m), 2.10 (3H, br s), 2.00 (2H, m), 1.78-1.13 (20H, m). The acid was converted to the N-methyl-D-glucamine salt and lyophilised from water/dioxan. Found: C 59.11, H 8.00, N 9.67%; $C_{35}H_{51}N_5O_8 \cdot 2.4 H_2O$ requires: C 59.00, H 7.89, N 9.83%.

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Example 4

2- [5-(Adamantan-1-yloxymethyl)-2-cyclohexyl -1H-imidazole-4-yl]-1H- benzoimidazole-4-carboxylic acid

- 10 **Step a.** *2,3-Diamino-benzoic acid methyl ester.* To a solution of 2-amino-3-nitro-benzoic acid methyl ester (Denny et al.: J. Med. Chem, 1990, **43**, 814) (500mg, 2.54mmol) in ethanol (25ml) was added 10% palladium on charcoal (100mg). The mixture was stirred under hydrogen atmosphere for 48h. The catalyst was filtered and the filtrate was evaporated to afford the product (316mg, 75%). 1H NMR (300 MHz, $CDCl_3$) 7.47 (1H, 15 dd), 6.85 (1H, dd), 6.60 (1H, t), 4.50 (4H, br s), 3.87 (3H, s).

- Step b.** *2-[5-(Adamantan-1-yloxymethyl)-1-benzyl-2-cyclohexyl -1H-imidazole-4-yl]-1H-benzoimidazole-4-carboxylic acid methyl ester.* To a solution of 5-(adamantan-1-yloxymethyl)-1-benzyl-2-cyclohexyl -1H-imidazole-4-carbaldehyde (Example 1, step f) 20 (430mg, 1.00mmol) in ethanol (5ml) was added 2,3-diamino-benzoic acid methyl ester (316mg, 1.90mmol). The mixture was heated at reflux for 2h. The solvent was evaporated, the residue was dissolved in nitrobenzene (5ml) and placed in an oil bath at 150°C for 1h. The solution was cooled to ambient temperature and purified by flash column chromatography (silica, DCM/ethyl acetate 9:1 to 8:2) to afford a colourless foam (184mg, 25 31%). 1H NMR (300 MHz, $CDCl_3$) 10.92 (1H, s), 7.93 (1H, d), 7.86 (1H, m), 7.30 (4H,m), 7.06 (2H, m), 5.36 (2H, s), 5.08 (2H, 2s), 4.03 (3H, s), 2.56 (1H, m), 2.12 (3H, br s), 1.80-1.54 (19H, m), 1.29 (3H, m).

- Step c.** *2-[5-(Adamantan-1-yloxymethyl)-2-cyclohexyl -1H-imidazole-4-yl]-1H-benzoimidazole-4-carboxylic acid methyl ester.* The product of step b (180mg, 0.31mmol) 30 was hydrogenolysed using essentially the same procedure as in Example 1, step i to afford an off-white solid (138mg, 91%). 1H NMR (300 MHz, $CDCl_3$) 12.33 (1H, br s), 11.25 (1H,

br s), 7.91 (2H, d), 7.31 (1H, t), 4.94 (2H, br s), 4.03 (3H, s), 2.79 (1H, m), 2.20-1.30 (25H, m).

Step d. The product of step c (131mg, 0.27mmol) was deprotected using essentially the same procedure as in Example 3, step c to afford off-white solid (98mg, 77%). ¹H NMR (300 MHz, d₆-DMSO) 7.76 (2H, m), 7.27 (1H, s), 4.89 (2H, br s), 2.74 (1H, m), 2.10 (3H, br s), 1.95-1.58 (19H, m), 1.40-1.21 (3H, m). The acid was converted to the N-methyl-D-glucamine salt and lyophilised from water/dioxan. Found: C 57.25, H 7.90, N 9.83%; C₃₅H₅₁N₅O₈·3.4 H₂O requires: C 57.50, H 7.97, N 9.58%.

10

Example 5

{2-[5-(Adamantan-1-yloxymethyl)-2-cyclohexyl -1H-imidazole-4-yl]- benzooxazol-5-yl}-acetic acid

15 The title compound was prepared according to the procedure of Example 1, with the modification that (3-amino-4-hydroxy-phenyl)-acetic acid methyl ester (prepared in two steps from (4-hydroxy-3-nitro-phenyl)-acetic acid) was used in step g instead of 3-amino-4-hydroxy-benzoic acid methyl ester. ¹H NMR (300 MHz, d₆-DMSO) 12.30 (2H, br s), 7.59 (2H, m), 7.21 (1H, d), 4.86 (2H, s), 3.68 (2H, s), 2.75 (1H, m), 2.11 (3H, br s), 1.92 (2H, m), 1.79-1.49 (17H, m), 1.28 (3H, m). The acid was converted to the N-methyl-D-glucamine salt and lyophilised from water/dioxan. Found: C 58.39, H 7.90, N 7.61%; C₃₆H₅₂N₄O₉·3.1 H₂O requires: C 58.44, H 7.92, N 7.57%.

25 The compounds of the examples were tested for gastrin (CCK₂) antagonist activity in an immature rat stomach assay. The procedure was as follows:

The oesophagus of immature rats (33-50 g, ca. 21 days old) was ligated at the level of the cardiac sphincter and the duodenal sphincter was cannulated. The stomach was excised and flushed with ca. 1 ml of unbuffered physiological saline solution. The fundus was punctured and cannulated. A further 4-5 ml of unbuffered solution was flushed through the stomach to ensure the preparation was not leaking. The stomach was lowered into a jacketed organ bath containing 40 ml of buffered solution containing 3 x 10⁻⁸ M 5-

methylnmethide, maintained at 37° and gassed vigorously with 95% O₂ / 5% CO₂. The stomach was continuously perfused at a rate of 1 ml min⁻¹ with unbuffered solution gassed with 100% O₂ with the perfusate passing over an internally referenced pH-electrode fixed 12 cm above the stomach.

5

After 120 min of stabilisation the drugs were added directly to the serosal solution in the organ bath and after a further 60 min cumulative pentagastrin dose-response curves were started. Changes in acid secretion were monitored and the curves analysed according to Black *et al.*, *Br. J. Pharmacol.*, 1985, **86**, 581.

10

The results obtained at gastrin (CCK₂) receptors are set out in Table 1.

Table 1

Example	Rat Stomach pK _B
1	5.48±0.31
2	5.79±0.15
3	5.47±0.23
4	6.43±0.35
5	5.69±0.20

15

It is found that the compositions and products of the present invention comprising a compound of formula (I) and a proton pump inhibitor reduce hyperplasia, associated with administration of proton pump inhibitors. This was measured according to the following experimental protocol.

20

Animals and treatment:

40 male SPF Wistar rats (200 g) were divided into 4 treatment groups and 2 strata. The treatment of the 20 rats in the second stratum started 2 weeks after the treatment of the first stratum. The design of the study was completely randomised double blind with individual

25

blinding; all rats were placed in a separate cage. Animals had continuous access to water and food.

Animals were treated once daily during 14 days:

- 5 - Control group: 1 ml gastrin test drug vehicle + 1 ml p.o.(gavage) 0,25% Methocel (Dow Corning)
- PPI group: 1 ml gastrin test drug vehicle +1 ml p.o.(gavage) 25 mg/kg Rabeprazole in 0.25% Methocel.
- GRA group: 1 ml gastrin test drug + 1 ml p.o. (gavage) 0,25% Methocel
- 10 - GRA-PPI group: 1 ml gastrin test drug + 1 ml p.o.(gavage) 25 mg/kg Rabeprazole in 0.25% Methocel.

Gastrin test drug made up to an appropriate dose in physiologically compatible solvent.

15 Preparation of tissue:

After removal of the fundus, the stomach were rinsed with phosphate buffered saline prior to fixation with 4% formalin in Millonig buffer. After 4 hours immersion in fixative solutions at room temperature, tissue was rinsed in phosphate buffered saline (PBS), dehydrated and embedded in paraffin using the Leitz paraffin embedding station (Leitz TP 20 1050; Germany) dehydration module and paraffin embedding module (Leitz EG 1160; Germany).

Cross sections (3 μm thick) of the oxyntic part of the stomach were made at 3 levels, each separated by a distance of 400 μm .

25

Immunostaining

The following indirect immunofluorescence labeling method was used:

- removal of paraffin and rehydration of the sections followed by a blocking step
 - primary antibodies: polyclonal guinea pig anti-histidine decarboxylase, 1/2000 (from Euro-Diagnostica) and monoclonal mouse anti PCNA 1/2500 (Clone PC10 from Sigma).
- 30 All antibodies were diluted in a 0.2% BSA solution. Sections were incubated overnight at 4°C and then washed with a BSA solution.

- secondary antibodies: goat anti guinea pig coupled to CY5, 1/500 (from Jackson Laboratories) and goat anti-mouse coupled to Cy3, 1/250 (from Jackson Laboratories); incubation for 4 hours at 37°C. After rinsing with BSA and PBS solutions, sections were mounted with slowfade (Molecular Probes Europe BV), and stored at 4°C.

5

Imaging

Fluorescence labelling was observed with an epifluorescence microscope or a Zeiss LSM510 (Carl Zeiss Jena GmbH) confocal microscope.

- 10 By using CY5- and CY3-coupled antibodies, the high autofluorescence properties of the oxyntic mucosa were circumvented when sections are illuminated by a 488 nm (FITC channel) light source. Negative controls, by omitting the primary antibodies, and an isotype control staining for PCNA showed complete absence of staining. The specific labelling of PCNA was checked using double staining with TOPRO-3® (Molecular Probes Europe
15 BV), a nuclear stain. Only in the most luminal located epithelial cells, non-specific cytoplasmic labelling was present. In the glandular part of the mucosa, non-specific PCNA-staining was absent.

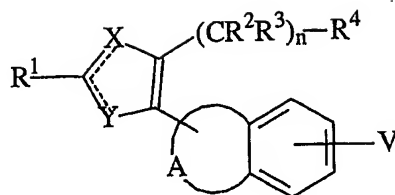
For determination of the labelling index of ECL cells, at least 80 confocal images per rat
20 were taken from the 3 slides at the 3 different levels. The ratio of double labelled cells (HDC + PCNA) and all HDC labelled cells yielded the labelling index of ECL cells.

Proliferation activity of ECL cells in the PPI group is expected to be increased compared with sham, GRA and GRA-PPI groups (Eissele, R., Patberg, H., Koop, H., Krack, W.,
25 Lorenz, W., McKnight, A.T., and Arnold, R. Effect of gastrin receptor blockade on endocrine cells in rats during achlorhydria. *Gastroenterology*, 103, 1596-1601, 1992). Increased proliferation by PPI will be completely blocked by GRA.

30

CLAIMS

1. A compound of formula (I)



(I)

5

wherein

X and Y are independently =N-, -N(R⁵)- (R⁵ being selected from H, Me, Et, Pr, Bn, OH and -CH₂COOR⁶, wherein R⁶ represents H, Me, Et, Pr or Bn), =CH-, -O- or -S-;
n is from 1 to 4;

- 10 A is an optionally substituted 5- or 6-membered carbocyclic ring wherein

- (a) 1 or 2 C atoms may optionally be replaced by N, O and/or S atoms,
- (b) A is fused with the aromatic group in formula (I) to form a fused bicycle, and
- (c) the ring containing X and Y is linked to a C atom of A;

- 15 R¹ is H or C₁ to C₁₅ hydrocarbyl wherein up to three C atoms may optionally be replaced by N, O and/or S atoms and up to three H atoms may optionally be replaced by halogen atoms;

R² is selected from H, Me, Et, Pr and OH, each R² being independently selected from H, Me, Et, Pr and OH when n is greater than 1;

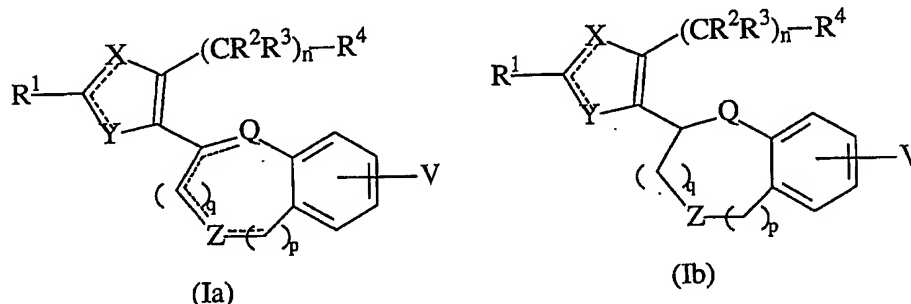
- 20 R³ (when n is 1) is selected from H, Me, Et and Pr; or (when n is greater than 1) each R³ is independently selected from H, Me, Et and Pr, or two R³ groups on neighbouring carbon atoms are linked to form a C₃ to C₆ carbocyclic ring, or two R³ groups are absent from neighbouring carbon atoms which are linked by a double bond; or R² and R³ on the same carbon atom together represent an =O group;

- 25 R⁴ is C₁ to C₁₅ hydrocarbyl wherein up to two C atoms may optionally be replaced by N, O and/or S atoms and up to three H atoms may optionally be replaced by halogen atoms;

V is -CO-NH-SO₂-Ph, -SO₂-NH-CO-Ph, -CH₂OH, or a group of the formula -R⁷U, (wherein U is -COOH, tetrazolyl, -CONHOH or -SO₃H; and R⁷ is a bond; C₁ to C₆ hydrocarbylene, optionally substituted by hydroxy, amino or acetamido;

$-\text{O}-(\text{C}_1 \text{ to } \text{C}_3 \text{ alkylene})-$; $-\text{SO}_2\text{NR}^8-\text{CHR}^9-$; $-\text{CO}-\text{NR}^8-\text{CHR}^9-$, R^8 and R^9 being independently selected from H and methyl; or $-\text{NH}-(\text{CO})_c-\text{CH}_2-$, c being 0 or 1); or a pharmaceutically acceptable salt thereof.

- 5 2. A compound according to claim 1 which is defined by formula (Ia) or (Ib).



wherein

X , Y , n , R^1 , R^2 , R^3 , R^4 and V are defined as in claim 1;

10 $p = 0$ or 1 ;

$q = 0$ or 1 ;

Z and Q are independently $=\text{N}-$, $-\text{NH}-$, $=\text{CH}-$, $-\text{CH}_2-$, $-\text{S}-$ or $-\text{O}-$; provided that

$p + q \neq 2$; and

when $p + q = 1$ in formula (Ia), at least one of Z or Q is $=\text{N}-$ or $=\text{CH}-$.

15

3. A compound according to claim 1 or 2 wherein the fused bicyclic is derived from naphthalene, benzimidazole, benzoxazole, benzothiazole, benzothiophene, isobenzothiophene, benzofuran, isobenzofuran, indole, isoindole, chromene, isochromene, quinoline, isoquinoline, quinoxaline, quinazoline, chroman, isochroman, indoline or
20 isoindoline.

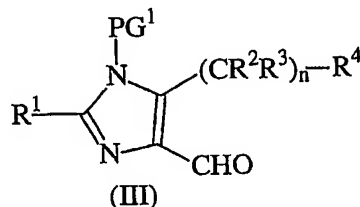
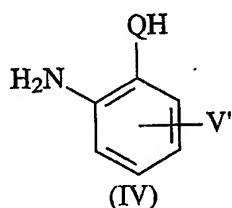
4. A compound according to any preceding claim wherein X is $=\text{NH}-$ and Y is $-\text{NH}-$, or *vice versa*.

- 25 5. A compound according to any one of claims 2 to 4 wherein p is 0; q is 0; Q is $=\text{N}-$; and Z is $-\text{NH}-$ or $-\text{O}-$.

6. A compound according to any preceding claim wherein R^1 is C_3 to C_{12} alicyclic; phenyl, pyridyl, phenyl C_1 - C_3 alkyl or pyridyl C_1 - C_3 alkyl (all optionally substituted with OMe, NMe₂, CF₃, Me, F, Cl, Br or I); or C_1 to C_8 alkyl.
- 5 7. A compound according to any preceding claim wherein R^1 is cyclohexyl or bicyclooctyl.
8. A compound according to any preceding claim wherein V is $-\text{CO}-\text{NH}-\text{SO}_2-\text{Ph}$, $-\text{SO}_2-\text{NH}-\text{CO}-\text{Ph}$, $-\text{OCH}_2\text{COOH}$, tetrazolyl or $(\text{CH}_2)_s\text{COOH}$, wherein s is from 0, 1 or 2.
- 10 9. A compound according to any preceding claim wherein V is CH_2COOH , COOH or tetrazolyl.
10. A compound according to any preceding claim wherein R^2 and R^3 are H, and n is
15 from 1 to 3.
11. A compound according to any preceding claim wherein R^2 and R^3 together form an $=\text{O}$ group and n is 1.
- 20 12. A compound according to any preceding claim wherein R^4 is C_3 to C_{15} carbocyclic.
13. A compound according to claim 12 wherein R^4 is adamantyl, cycloheptyl, cyclohexyl or phenyl.
- 25 14. A compound according to any one of claims 1 to 11 wherein R^4 is $-\text{NH}-R^{10}$ or $-\text{OR}^{10}$, in which R^{10} is C_3 to C_{10} carbocyclic.
15. A compound according to claim 14 wherein R^{10} is adamantyl, cycloheptyl, cyclohexyl or phenyl.
- 30 16. A compound which is degraded *in vivo* to yield a compound according to any one of the preceding claims.

17. A method of making a compound according to formula (Ia) wherein
- (i) p is 0
 - (ii) q is 0
 - 5 (iii) X is -NH-
 - (iv) Y is =N-
 - (v) Q is -O- or -NH-
 - (vi) Z is =N-

including the step of reacting a compound of formula (III), or a suitably protected derivative thereof, with a compound of formula (IV), or a suitably protected derivative thereof,



followed by heating and oxidation of the resultant imine, with concomitant cyclisation.

- 15 18. A pharmaceutical composition comprising a compound according to any one of claims 1 to 16 together with a pharmaceutically acceptable diluent or carrier.
19. A pharmaceutical composition comprising a proton pump inhibitor and a compound according to any one of claims 1 to 16 together with a pharmaceutically
- 20 acceptable diluent or carrier.
20. A composition according to claim 19 wherein the proton pump inhibitor is selected from (RS)-rabeprazole, (RS)-omeprazole, lansoprazole, pantoprazole, (R)-omeprazole, (S)-omeprazole, perprazole, (R)-rabeprazole, (S)-rabeprazole, or the alkaline salts thereof.
- 25 21. A composition according to claim 19 or 20 wherein the proton pump inhibitor and the compound of formula (I) are each in an amount producing a therapeutically beneficial effect in patients suffering from gastrointestinal disorders.

22. A composition according to claim 21 wherein said therapeutically beneficial effect is a synergistic effect on the reduction of acid secretion in patients suffering from gastrointestinal disorders, or the prevention of gastrointestinal disorders in said patients, or
5 the reduction of adverse effects associated with the one of the active ingredients by the other active ingredients.
23. A composition according to any one of claims 19 to 22 wherein the amount of each of the active ingredients is equal to or less than that which is approved or indicated in
10 monotherapy with said active ingredient.
24. A product containing as first active ingredient a compound of formula (I) and as second active ingredient a proton pump inhibitor, as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from
15 gastrointestinal disorders.
25. A compound according to any one of claims 1 to 16, a composition according to any one of claims 18 to 23, or a product according to claim 24 for use in medicine.
- 20 26. A compound according to any one of claims 1 to 16, a composition according to any one of claims 18 to 23, or a product according to claim 24 for use in treating gastrointestinal disorders.
27. Use of a compound according to any one of claims 1 to 16, a composition according
25 to any one of claims 18 to 23 or a product according to claim 24 for the preparation of a medicament for the treatment of gastrointestinal disorders.
28. Use of a proton pump inhibitor for the preparation of a medicament for the treatment of gastrointestinal disorders, said treatment comprising the simultaneous or
30 sequential administration of said proton pump inhibitor and a compound of formula (I), wherein said proton pump inhibitor enhances the effect of the compound of formula (I) on gastrin-related disorders in patients suffering from gastrointestinal disorders.

29. Use of a compound of formula (I) for the preparation of a medicament for the treatment of gastrointestinal disorders, said treatment comprising the simultaneous or sequential administration of said proton pump inhibitor and a compound of formula (I),
5 wherein said compound of formula (I) enhances the effect of the proton pump inhibitor on the reduction of acid secretion in patients suffering from gastrointestinal disorders.
30. Use of a compound of formula (I) for the preparation of a medicament for reducing adverse effects associated with administration of proton pump inhibitors in patients
10 suffering from gastrointestinal disorders.
31. Use according to claim 30 wherein the adverse effect is hyperplasia.
32. Use of a proton pump inhibitor for the preparation of a medicament for reducing
15 adverse effects associated with administration of a compound of formula (I) in patients suffering from gastrointestinal disorders.
33. Use of a compound according to any one of claims 1 to 16, a composition according to any one of claims 18 to 23 or a product according to claim 24 in the treatment of
20 gastrointestinal disorders.
34. A method of making a pharmaceutical composition according to claim 18 comprising mixing a compound of formula (I) with a pharmaceutically acceptable diluent or carrier.
25
35. A method of making a pharmaceutical composition according to any one of claims 19 to 23, comprising mixing a compound of formula (I) and a proton pump inhibitor with a pharmaceutically acceptable diluent or carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/01982

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D413/04 C07D403/04 A61K31/42 A61K31/415 A61P1/04		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the International search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, BEILSTEIN Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	US 5 719 143 A (BADORC ET. AL.) 17 February 1998 (1998-02-17) column 1, line 1 - line 65; claims; examples	1-35
A	WO 93 12817 A (WARNER-LAMBERT) 8 July 1993 (1993-07-08) cited in the application claims; examples	1-35
-/--		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents: *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *G* document member of the same patent family		
Date of the actual completion of the international search 3 July 2001		Date of mailing of the international search report 13/07/2001
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Helps, I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/01982

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 1994, no. 92961 & JP 06 092961 A (SHIKOKU CHEMICAL CORPORATION), 5 April 1994 (1994-04-05) abstract ----	1-35
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A	E. LINDSTRÖM ET. AL.: "Pharmacological Analysis of CCK2 Receptor Antagonists Using Isolated Rat Stomach ECL Cells." BRITISH JOURNAL OF PHARMACOLOGY, vol. 127, 1999, pages 530-6, XP001000286 page 531, column 1, paragraph 2 -----	1-35

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Information on patent family members

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